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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,399	09/25/2003	Linda Pilarski	A894635US	1833

37047 7590 11/06/2006

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,399	PILARSKI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-28 and 49-105* is/are pending in the application.

4a) Of the above claim(s) *24-26,28,51-87 and 91-105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23,27,49,50 and 88-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *exhibit A*.

Request Continued Examination (RCE)

The request filed on 2/28/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10672399 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 1-20, 22, 29-48 106-107 have been cancelled. Claims 21, 23-28 and 49-105 are pending Claims 24-26, 51-87 and 91-105 have been withdrawn previously as non-elected invention. It is noted claim 28 has been amended previously to "detection of single nucleotide conversion of base 924 of HAS1, SEQ ID NO: 1", which is not elected species and is withdrawn as non-elected invention at this time. Claims 21, 23, 27, 49-50, and 88-90 extended to species HAS1Va (SEQ ID NO: 3) are under consideration.

Previous final Office Action dated 11/30/05

The rejections in the previous Office action, dated 11/30/05 are withdrawn. **If any rejection/objection is maintained, it will be stated again below.**

Priority

This application claims benefit of U.S. provisional application No. 60/472401, filed on 5/20/2003, which is acknowledged.

Objection of Drawing

The informal drawings are not of sufficient quality to permit examination. Accordingly, replacement drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action.

Figure 9 is objected to because the quality of the figure is not permitted for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the **second paragraph of 35 U.S.C. 112**:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23, 27, 49-50, and 88-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite in the recitation of "HAS1 isoenzyme variants" or "HAS1Va" in claims 21, 23, 28, 49, and 88. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Further, it is unclear if HAS1Va is the same or different as nucleotide sequence SEQ ID NO: 3. This rejection can be obviated by amending the claims to specifically and uniquely identify HAS1, for example, by SEQ ID NO.

The following is a quotation of the **first paragraph** of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As drawn to scope of enablement:

Claims 21, 23, are 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for detecting gene expression of HAS1Va, SEQ ID NO: 3, encoding a protein having amino acid sequence SEQ ID NO: 4 by PCR with oligonucleotide primers, SEQ ID NO: 9 and SEQ ID NO:10, does not reasonably provide enablement for a method for detecting other HAS1 isoenzyme variants by using this set of primers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The method objective of claims is detecting HAS1 isoenzyme variants by PCR using oligonucleotide primers of SEQ ID NO: 9 and SEQ IDNO: 10. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. Thus, it would be expected that one of skill in the art would be able to detect all the HAS1 isoenzyme variants without undue experimentation by using the claimed method.

The specification discloses HAS1 isoenzyme variants HAS1Va, HAS1Vb, and HAS1Vc having a DNA sequence of SEQ ID NO: 3, 5, and 7. The specification discloses a method of On-chip PCR using oligonucleotide primers of SEQ ID NO: 9 and SEQ ID NO: 10 for HAS1Va (page 51-52). The specification, in example 1, discloses a method of detecting HAS1 variants by RT-PCR, but no primers are disclosed. HAS1 isoenzyme variants, understood by one skilled in the art, include a large numbers of variants alternated from wild type of HAS1 gene. The variants of HAS1 would include mutated, deleted, or inserted forms of the gene products, in which the nucleotide sequences could have been already defined and not been defined yet in the art. These variants would be structural and sequence different gene products, in which the sequence may be altered at any place of the gene or gene product. Using designed set of primers (SEQ ID NO: 9 and SEQ ID NO: 10) according to HAS1Va DNA sequence may only detect HAS1Va having a sequence of SEQ ID NO: 3 or any deletion or insertion of nucleotides between the binding sites of the primers in the SEQ ID NO: 3 with a confirmation of sequencing the detected fragment. Detection of other insertion, deletion, or mutation at any other place of HAS1Va or any other HAS1 by PCR with this set of primers is not enabled and must be undue experimentation with the new primer set. For example, the specification discloses three variants of HAS1V, HAS1Va (SEQ IDNO: 3), HAS1Vb (SEQ IDNO: 5), and HAS1Vc (SEQ ID NO:7). The primers (SEQ ID NO: 9 and SEQ

ID NO: 10) will detect a fragment of HAS1Va (SEQ ID NO: 3) between nucleotide 876-966, which is not even present in the HAS1Vc (SEQ ID NO: 7, see sequence search exhibit A). Accordingly, any other variants of HAS1 having nucleotide changes beyond than the nucleotide sequence between 876-966 would not be detectable with the set of the primers (SEQ ID NO: 9 and SEQ ID NO: 10). Applicants have not provided any teaching on any other specific variant of HAS1 being detected by the method using primer of SEQ ID NO: 9 and SEQ ID NO:10.

In the absence of this minimal structure or sequence of variants of HAS1, In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the method of detecting expression of HAS1 isoenzyme variants other than HAS1Va with primers SEQ ID NO: 9 and SEQ ID NO:10, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention. If Applicants has any objective evidence contrary to the rejection, Applicant is invited to submit it to the Office for consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 88 and 90 are rejected under 35 U.S.C. 102(a) as being anticipated by Adamia et al., (Seminars in Oncology, Vol 30, page 165-168, April 2003, provided in previously office action).

1. Adamia et al., disclose a method of monitoring malignant cells of Waldenstrom's Macroglomulemia (WM) patients by detecting aberrant expression of HAS1 isozyme variants in bone marrow cells from WM patients. Adamia et al., disclose that overexpression of HAS isozyme variants contribute to malignant growth and spread in WM patients and also disclose expression patterns of the HAS gene promote migration of the WM cells in the patients (page 165, abstract, page 166 table 1).

2. Claims 49-50 and 88-89 are rejected under 35 U.S.C. 102(a) as being anticipated by Calabro et al., (Blood, vol 100; page 2578-2585, Oct, 2002, provided in previous office action).

Calabro et al., disclose a method of determining malignancy and monitoring malignant cells in multiple myeloma (MM) patient by detecting HAS isoenzyme variant gene product, specifically mRNA expression in the bone marrow plasma cells from MM patient's bone marrow aspirates (page 2579, column 1, paragraph 1). Calabro et al., disclose that MM is a malignancy characterized by the accumulation of malignant plasma cells within the bone marrow (page 2578, column 1, paragraph 2). Calabro et al., further disclose that HAS1 isoenzyme variant mRNA is expressed predominantly in the myeloma bone marrow plasma cells from MM patient compared with normal bone marrow cells (figure 1, and page 2582, column 1, paragraph 2).

Because the term" likelihood of poor clinical outcome in a human suffering from MM" in claim 49 is not specifically defined, the pathological condition of MM is considered as poor clinical outcome. Thus, the teaching on "HAS1 isoenzyme variant mRNA is expressed predominantly in the myeloma bone marrow plasma cells from MM patient compared with normal bone marrow cells" in the reference anticipates the claimed invention.

Conclusion

No claims are allowed.

Claim 21, 23 and 27 are free of art. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Calabro et al., (Blood, vol 100, page 2578-2585, Oct, 2002) teach a method of detecting expression of HAS1 isoenzyme variants using PCR.. Calabro et al., do not teach or suggest the method using oligonucleotide primers of SEQ ID NO: 9 and SEQ ID NO:10.

2. Venter et al., (US Patent NO: 6812339) teach a DNA encoding a protein having 99.4% amino acid identity to HAS1Va. The DNA taught by Venter et al., comprises a primer sequence of SEQ IDNO: 9 and the complement of the DNA comprise SEQ IDNO:10. Venter et al., do not teach or suggest a

method of detecting expression of HAS1Va using oligonucleotide primers of SEQ ID NO: 9 and SEQ ID NO:10.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

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Qy        421 GACCTCTACATGGTCGACATGTTCCGCGAGGTCTTCGCTGACGAGGACCCCGCCACGTAC 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        841 AGCAGCCTGCGATACTGGGTAGCCTTCAATGTGGAGCGGGCTTGTCAGAGCTACTTCCAC 900
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Qy        927 -------------------------AGGTACACCTCCAGGTCCCGCTGCTACTCAGAGAC 961
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Qy       1022 TGA 1024
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Db       1081 TGA 1083
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RESULT 3
US-10-672-399-7
; Sequence 7, Application US/10672399
; GENERAL INFORMATION:
; APPLICANT: University of Alberta
; TITLE OF INVENTION: Cancer Monitoring and Therapeutics
; FILE REFERENCE: A894635US
; CURRENT APPLICATION NUMBER: US/10/672,399
; CURRENT FILING DATE: 2003-09-25
; PRIOR APPLICATION NUMBER: US 60/472,401
; PRIOR FILING DATE: 2003-05-22
; NUMBER OF SEQ ID NOS: 14
; SOFTWARE: PatentIn version 3.2
; SEQ ID NO 7
; LENGTH: 1065
; TYPE: DNA
; ORGANISM: Homo sapiens
US-10-672-399-7

Exhibit A

1 C

Query Match 86.6%; Score 927.4; DB 58; Length 1065;
Best Local Similarity 99.9%; Pred. No. 5.5e-139;
Matches 928; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

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Qy        361 CTGCTGTACCCGCGCGCGCGGCTGCGCGTCCTCATGGTGGTGGATGGCAACCGCGCCGAG 420
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Qy        781 GGGGCTGTTGGTGGGGACGTGCGGATCCTTAACCCTCTGGACTCCTGGGTCAGCTTCCTA 840
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RESULT 4
PCT-US02-41225A-223

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;  FILE REFERENCE: GX-0022 PCT
;  CURRENT APPLICATION NUMBER: PCT/US02/41225A
;  CURRENT FILING DATE:  2003-03-20
;  PRIOR APPLICATION NUMBER: US 60/342,603
;  PRIOR FILING DATE: 2001-12-20
;  NUMBER OF SEQ ID NOS: 499
;  SOFTWARE: PERL Program
; SEQ ID NO 223
;   LENGTH: 1737
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: misc_feature
;   OTHER INFORMATION: Incyte ID No: GB:NM_001523.1
PCT-US02-41225A-223

  Query Match             86.6%;  Score 927.4;  DB 1;  Length 1737;
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  Matches  928;  Conservative    0;  Mismatches    1;  Indels    0;  (
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Qy          1 ATGAGACAGCAGGACGCGCCCAAGCCCACTCCTGCAGCCCGCCGCTGCTCCGGCC
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Qy         61 CGGAGGGTGCTGACCATCGCCTTCGCCCTGCTCATCCTGGGCCTCATGACCTGGG
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Db         61 CGGAGGGTGCTGACCATCGCCTTCGCCCTGCTCATCCTGGGCCTCATGACCTGGG

Qy        121 GCCGCCGGGGTGCCGCTGGCCTCCGATCGCTACGGCCTCCTGGCCTTCGGCCTCTA
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Qy        181 GCCTTCCTTTCAGCGCACCTGGTGGCGCAGAGCCTCTTCGCGTACCTGGAGCACCC
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Qy        361 CTGCTGTACCCGCGCGCGCGGCTGCGCGTCCTCATGGTGGTGGATGGCAACCGCGC
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Qy        421 GACCTCTACATGGTCGACATGTTCCGCGAGGTCTTCGCTGACGAGGACCCCGCCAC
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 GACCTCTACATGGTCGACATGTTCCGCGAGGTCTTCGCTGACGAGGACCCCGCCAC

Qy        481 GTGTGGGACGGCAACTACCACCAGCCCTGGGAACCCGCGGCGGCGGGCGCGGTGGG
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 GTGTGGGACGGCAACTACCACCAGCCCTGGGAACCCGCGGCGGCGGGCGCGGTGGG

Qy        541 GGAGCCTATCGGGAGGTGGAGGCGGAGGATCCTGGGCGGCTGGCAGTGGAGGCGCT
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 GGAGCCTATCGGGAGGTGGAGGCGGAGGATCCTGGGCGGCTGGCAGTGGAGGCGCT

Qy        601 AGGACTCGCAGGTGCGTGTGCGTGGCGCAGCGCTGGGGCGGCAAGCGCGAGGTCAT
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 AGGACTCGCAGGTGCGTGTGCGTGGCGCAGCGCTGGGGCGGCAAGCGCGAGGTCAT

Qy        661 ACAGCCTTCAAGGCGCTCGGAGATTCGGTGGACTACGTGCAGGTCTGTGACTCGGA
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 ACAGCCTTCAAGGCGCTCGGAGATTCGGTGGACTACGTGCAGGTCTGTGACTCGGA
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